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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Didier Trono

CLFR:023US

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05/25/2006

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EXAMINER

ASHEN, JON BENJAMIN

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 05/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	10/720,987	TRONO ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 26 February 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-7, 9-11, 13, 41, 46 and 47 is/are pending in the application.
- 4a) Of the above claim(s) 8, 12, 14-40, 42-45 and 48-84 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9-11, 13, 41, 46 and 47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>2/27/2006</u> | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

1. Claims 1-84 are pending in this application. Claims 8, 12, 14-40, 42-45 and 48-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-7, 9-11, 13, 41, 46 and 47 are currently under examination.

Applicant's response filed 2/27/2006 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 12/12/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Information Disclosure Statement***

2. Applicant has noted that references C70-C303 were previously submitted and received by the PTO and pointed to an enclosed copy of a postcard that they assert shows that the references were received by the PTO. It is noted here that, although no copy of this postcard could be located in the Application file, Applicant has submitted copies of references C70-C303 that were referred to on the IDS filed 2/26/2004, which references have now been considered. References C86 to C89, which list Genbank

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Accession numbers w/o dates, are in improper format and have therefore not been considered.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 41, 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 41 has been amended to recite, "wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain, said polypeptide regulator being encoded by said cell." However, upon review of the specification as filed, no support could be located for the limitation wherein the required polypeptide regulator is encoded by said cell. Additionally, Applicant has not pointed out, in their remarks, where support for the instant claims amendments may be found in the instant specification (pg. 17, remarks).

5. Claims 1-7, 9-11, 13, 41 and 46-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

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contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-7, 9-11, 13, 41 and 46-47 are broadly drawn to polynucleotide constructs that encode siRNAs operably linked to externally controllable promoters wherein expression of the wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain. However, the specification as filed does not provide an adequate written description of the broad genera of constructs as claimed, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain wherein that polypeptide regulator can be any polypeptide regulator.

The specification as filed provides no definition or description of what is meant or encompassed by the terminology, polypeptide regulator and provides no structure of a polynucleotide construct as claimed, that expresses an siRNA that is regulated by a polypeptide regulator that can be any polypeptide regulator, that will function commensurate with what is now claimed, to control the expression of an siRNA polynucleotide construct.

However, the general description and few examples provided by the specification are insufficient to indicate possession of the broadly claimed genera of constructs as claimed. The specification does not provide the specific description that would be required to allow the skilled artisan to recognize that Applicant was in possession of the

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broad genera as claimed or to recognize that Applicant was in possession of a representative number of species of broad genera of constructs as claimed.

Additionally, the state of the art cannot provide the required written description because the state of the art is silent with regards to the terminology, polypeptide regulator, as used in the context of the instant claims.

What is the structure of a construct that encodes an siRNAs operably linked to any externally controllable promoter wherein expression of the siRNA is regulated by any polypeptide regulator having both a DNA binding domain and a repressor domain, that will function, commensurate with what is claimed, to regulate the expression of the encoded siRNA, for example?

MPEP § 2163[R-2] I. states:

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); < Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or

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disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of what is now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of a representative number of species of constructs as claimed or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the broad genus of constructs as claimed.

#### ***Claim Rejections - 35 USC § 101***

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 41, 46 and 47 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. In the instant case, the claims read on transgenic humans.

#### ***Claim Rejections - 35 USC § 103***

8. Claims 1-7, 9-11, 13, 41 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yao et al. (W0 99/00510), Verma et al. (US Patent 6,013,516; Reference A23 on PTO Form 1449 filed 02/26/04), Elbashir et al. (EMBO Journal, Vol.,

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20(23):6877-6888; published December 3<sup>rd</sup> 2001), Elbashir et al. 2001 (Nature Vol., 411: pp. 494-498) and Deuschle et al. 1995 (Mol. Cell. Biol. Vol. 15(4): p. 1907-1914; Reference C63 on PTO Form 1449 filed 02/26/04).

Claims 1-7, 9-11, 13, 41 and 46-47 are drawn to a polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable promoter (claim 1) that is a vector (claim 2) that is a lentiviral vector (claim 3) wherein the promoter is repressible by means of an externally applied agent that is an externally applied drug (claims 4-5) wherein the repressible promoter is regulated by a Tet repressor and comprises at least one *tetO* sequence (claims 6-7) and is from the TeT<sup>R</sup> gene (claim 9) wherein the promoter is an inducible promoter by means of an externally applied agent that is tetracycline or tetracycline analogue (claims 10-11) wherein the inducible promoter is inducible as listed in claim 13 and to a mammalian cell comprising the polynucleotide construct of claim 1 (claim 41) wherein the cell is an undifferentiated cell (claim 46) or an oocyte (claim 47)

Yao et al. teach DNA constructs suitable for gene expression in mammalian cells which are characterized by the presence of a mammalian promoter under control of a Tet operator/repressor system and that this Tet operator/repressor system can be used to engineer viruses as vehicles for the delivery of nucleic acids that can serve as therapeutic agents including antisense nucleic acids that bind and inhibit protein expression (Abstract, pg. 2, line 20 – pg. 3, line 17; pg. 20 "D"). Yao et al. teach recombinant DNA molecules, the expression of which is under control of a repressible or inducible mammalian promoter that is regulated by a Tet operator sequence (pg. 13,

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lines 4-25). Yao et al. teach the typical incorporation of their polynucleotide constructs into viral vectors that can be retroviruses (pg. 10, line 1). Yao et al. teach the transduction of mammalian stem cells with the polynucleotide constructs and vectors of their invention (pg. 15). Yao et al. teach that by combining transdominant negative mutant viral polypeptides with the Tet<sup>R</sup>-regulated potent mammalian transcription switch, a novel viral replication switch can be generated and that in principle, any polypeptide or antisense RNA that is capable of inhibiting viral productive infection can be incorporated into the novel viral replication switch. The disclosure of Yao et al., therefore, is reasonably considered a disclosure of a polynucleotide construct that expresses a nucleic acid therapeutic that can be an antisense RNA wherein the expressed nucleic acid is operably linked to an externally controllable promoter that is a repressible promoter that can be down regulated by means of externally applied agent or drug (because the Tet operator can be down regulated by external application of doxycycline or the Tet repressor protein) that is regulated by a Tet repressor wherein the repressible promoter is from the Tet<sup>R</sup> gene (see figure 2, for example) and a disclosure of an inducible promoter that can be upregulated by an externally applied agent that is tetracycline.

Yao et al. do not teach the expression of siRNAs from the polynucleotide constructs of their invention or specifically recite lentiviral vectors or wherein the expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain.

Verma et al. (US Patent 6,013,516) disclose lentiviral vectors that express heterologous nucleic acid sequences that are operably linked to a regulatory nucleic acid sequence that can be a promoter and that a wide range of promoters, including suitable viral and mammalian promoters are known in the art (col. 6, lines 24-29). Verma et al. disclose that the lentiviral vectors of their invention can be used to express antisense nucleic acids and ribozymes to inhibit gene expression in mammalian cells (col. 7).

Elbashir et al. teach a systematic analysis of the length, secondary structure, sugar backbone and sequence specificity of siRNA duplexes used for RNAi in *Drosophila* and the structure of the most potent siRNA duplexes that are 21 nt long comprising a 19 nt base paired sequence with 2 nt 3' overhanging ends (see "siRNA users guide": pg. 6885). Elbashir et al. teach that siRNAs are valuable reagents for inactivation of gene expression, not only in insect cells but also in mammalian cells, with great potential for therapeutic application (pg. 6884, col. 2).

Elbashir et al. (Nature) teach that the mediators of sequence specific messenger RNA degradation in mammalian cells are 21 and 22 nucleotide small interfering RNAs, that 21 nucleotide siRNA duplexes specifically express expression of endogenous and heterologous genes in different mammalian cell lines and that therefore 21 nt siRNAs provide a new tool for studying gene function (Abstract). Elbashir et al. teach that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the

concentrations applied in conventional antisense or ribozyme gene targeting experiments (pg. 496, col. 2).

Deuschle et al. teach tetracycline reversible promoters that are controlled by a tetracycline controlled transrepressor protein that is a tetR-KRAB fusion protein that is reasonably considered to be a polypeptide regulator that comprises a DNA binding domain and a repressor domain (pg. 1907, col. 1-2). Deuschle et al. teach the tetR-KRAB silencing system useful as a genetic switch for regulating the expression of heterologous and endogenous genes, that their data offers a novel way to regulate gene expression in higher mammalian cells and that the tetR-KRAB fusion protein offers the unique possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation (Abstract, pg. 1913, col. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to formulate a polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable promoter that was a lentiviral vector construct wherein expression of the siRNA was regulated by a TetR-KRAB operator/repressor system (as taught by Yao et al., Elbashir et al., Verma et al. and Deuschle et al.) wherein the externally controllable promoter was repressible by means of an externally applied agent that is an externally applied drug, wherein the repressible promoter was regulated by a Tet repressor and comprises at least one *tetO* sequence and is from the  $Tet^R$  gene (as taught by Yao et al.) wherein the promoter is an inducible promoter by means of an externally applied agent that is tetracycline or tetracycline analogue (as taught by Yao et al.) in order to transduce mammalian stem

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cells (as taught by Yao et al.) to down regulate the expression of cellular genes on top of their normal regulation, thereby providing a specific means of studying gene function (as taught by Deuschle et al. and Elbashir et al.)

One of ordinary skill in the art would have been motivated to construct a polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable promoter that was a lentiviral vector construct wherein expression of the siRNA was regulated by a TetR-KRAB operator/repressor system in order to down regulate the expression of cellular genes on top of their normal regulation, thereby providing a specific means of studying gene function in a mammalian cell by controlling the expression of an siRNA (as taught by Elbashir et al., Yao et al., Verma et al.) and because Deuschle et al. teach the utility of the tetR-KRAB silencing system as a genetic switch for regulating the expression of heterologous and endogenous genes, that this system offers a novel way to regulate gene expression in higher mammalian cells and that the tetR-KRAB fusion protein offers the unique possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation.

One of ordinary skill in the art would have expected success in constructing a polynucleotide construct as above because all of the individual elements required by the claimed construct are were known and used successfully in the prior art of regulating the expression of cellular genes in mammalian cells, because the functional anatomy of siRNAs that are effective in mammalian cells was known, because the siRNAs described by Elbashir et al. provide a new tool for studying gene function, because siRNAs are extraordinarily powerful reagents for mediating gene silencing and are

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effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (as taught by Elbashir et al.), because Yao et al. teach the successful construction of the above polynucleotide construct in a retroviral vector, because lentiviral vectors are retroviral vectors that are taught by Verma et al. as viral vectors that will express heterologous nucleic acid sequences that are operably linked to a regulatory nucleic acid sequence that can be any of a wide range of promoters, including suitable viral and mammalian promoters that are known in the art, and Verma et al. teach that lentiviral vectors can be used to express antisense nucleic acids and ribozymes to inhibit gene expression in mammalian cells

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

9. Claims 1-7, 9-11, 13, 41 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giordano et al., Elbashir et al. 2001 (EMBO Journal), Elbashir et al. 2001 (Nature), Deuschle et al. and Verma et al. (US Patent 6,013,516). The invention set forth in the instant claims is relied upon as in a previous rejection above.

Giordano et al. (EP 1 229 134 A2; Reference B10 on PTO Form 1449 filed 11/12/2004) teach the use of inducible and repressible transcription systems that can be used to control the timing of the expression of dsRNA from polynucleotide constructs that can be retroviral vectors which express siRNAs wherein the inducible and

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repressible transcription system can be the previously described Tet promoter (see sections: [0110], [0010-0012], [0049-0050] and [0073]). The teachings of Giordano et al., of the Tet promoter inducible and repressible transcription system is reasonably considered an inherent disclosure of a repressible promoter regulated by the Tet repressor which comprises at least one *tetO* sequence (or it would not be repressible) that is antibiotic inducible by doxycycline (as known in the art, see previous rejection herein). Giordano et al. disclose the polynucleotide constructs of their invention as comprised in mammalian cells, stem cells and gametes (which is reasonably considered an inherent disclosure of both sperm and oocytes) (see section [0016]).

Elbashir et al. teach a systematic analysis of the length, secondary structure, sugar backbone and sequence specificity of siRNA duplexes used for RNAi in *Drosophila* and the structure of the most potent siRNA duplexes that are 21 nt long comprising a 19 nt base paired sequence with 2 nt 3' overhanging ends (see "siRNA users guide": pg. 6885). Elbashir et al. teach that siRNAs are valuable reagents for inactivation of gene expression, not only in insect cells but also in mammalian cells, with great potential for therapeutic application (pg. 6884, col. 2).

Elbashir et al. (Nature) teach that the mediators of sequence specific messenger RNA degradation in mammalian cells are 21 and 22 nucleotide small interfering RNAs, that 21 nucleotide siRNA duplexes specifically express expression of endogenous and heterologous genes in different mammalian cell lines and that therefore 21 nt siRNAs provide a new tool for studying gene function (Abstract). Elbashir et al. teach that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that

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siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (pg. 496, col. 2).

Deuschle et al. teach tetracycline reversible promoters that are controlled by a tetracycline controlled transrepressor protein that is a tetR-KRAB fusion protein that is reasonably considered to be a polypeptide regulator that comprises a DNA binding domain and a repressor domain (pg. 1907, col. 1-2). Deuschle et al. teach the tetR-KRAB silencing system as useful as a genetic switch for regulating the expression of heterologous and endogenous genes, that their data offers a novel way to regulate gene expression in higher mammalian cells and that the tetR-KRAB fusion protein offers the unique possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation (Abstract, pg. 1913, col. 2).

Verma et al. (US Patent 6,013,516) disclose lentiviral vectors that express heterologous nucleic acid sequences that are operably linked to a regulatory nucleic acid sequence that can be a promoter and that a wide range of promoters, including suitable viral and mammalian promoters are known in the art (col. 6, lines 24-29). Verma et al. disclose that the lentiviral vectors of their invention can be used to express antisense nucleic acids and ribozymes to inhibit gene expression in mammalian cells (col. 7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to formulate a polynucleotide construct comprising a region encoding a siRNA (as taught by Elbashir et al. ) operably linked to an externally

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controllable promoter that was a lentiviral vector construct wherein expression of the siRNA was regulated by a TetR-KRAB operator/repressor system (as taught by Giordano et al., Verma et al. and Deuschle et al.) wherein the externally controllable promoter was repressible by means of an externally applied agent that is an externally applied drug, wherein the repressible promoter was regulated by a Tet repressor and comprises at least one *tetO* sequence and is from the  $Tet^R$  gene wherein the promoter is an inducible promoter by means of an externally applied agent that is tetracycline or tetracycline analogue, in order to transduce mammalian stem cells (as taught by Giordano et al.) for the purposes of studying gene function, particularly in differentiating stem cells, by down regulating the expression of cellular genes on top of their normal regulation (as taught by Giordano et al., Elbashir et al. and Deuschle et al.).

One of ordinary skill in the art would have been motivated to construct the above polynucleotide construct in order to down regulate the expression of cellular genes on top of their normal regulation, thereby providing a specific means of studying gene function in a mammalian cell by controlling the expression of an siRNA (as taught by Giordano et al., Elbashir et al., Verma et al. and Deuschle et al.) and because Deuschle et al. teach the utility of the tetR-KRAB silencing system as a genetic switch for regulating the expression of heterologous and endogenous genes, that this system offers a novel way to regulate gene expression in higher mammalian cells and that the tetR-KRAB fusion protein offers the unique possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation.

One of ordinary skill in the art would have expected success in constructing the above polynucleotide construct because all of the individual elements required by the claimed construct are were known and used successfully in the prior art of regulating the expression of cellular genes in mammalian cells, because the functional anatomy of siRNAs that are effective in mammalian cells was known, because the siRNAs described by Elbashir et al. provide a new tool for studying gene function, because siRNAs are extraordinarily powerful reagents for mediating gene silencing and are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (as taught by Elbashir et al.), because Giordano et al. teach the successful construction of the above polynucleotide construct in a retroviral vector, because lentiviral vectors are retroviral vectors that are taught by Verma et al. as viral vectors that will express heterologous nucleic acid sequences that are operably linked to a regulatory nucleic acid sequence that can be any of a wide range of promoters, including suitable viral and mammalian promoters that are known in the art, and Verma et al. teach that lentiviral vectors can be used to express antisense nucleic acids and ribozymes to inhibit gene expression in mammalian cells. Therefore, one of skill would have expected success in formulating a retroviral vector for inducible or repressible control of expression of siRNAs in mammalian cells using the TetR-KRAB operator/repressor system (as taught by Deuschle et al. for example), wherein the mammalian cells were undifferentiated cells or oocytes (as taught by Giordano et al.)

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wherein the vector was a lentiviral vector known to be effective at delivering and expressing nucleic acids to mammalian cells (as taught by Verma et al.).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

10. Applicant's arguments, filed 2/27/2006, with respect to claims 1-7, 9-11, 13, 41 and 46-47 (pgs 18 –19) have been considered but are moot in view of the new ground(s) of rejection.

### ***Conclusion***

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4715. The fax phone number for the organization where this application or proceeding is assigned is 703-273-8300.

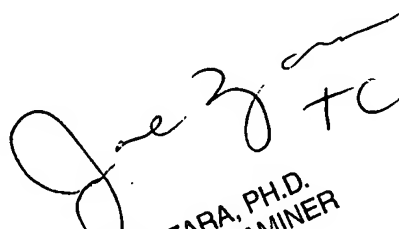
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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Jba

  
JANE ZARA, PH.D.  
PRIMARY EXAMINER  
TC1600